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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/048,186	06/19/2002	James C Liao	06497-013002	2905

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Fish & Richardson
225 Franklin Street
Boston, MA 02110-2804

EXAMINER

PROUTY, REBECCA E

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 06/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/048,186

Applicant(s)

LIAO, JAMES C

Examiner

Rebecca E. Prouty

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 April 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,5,11-13,17,21-24,37,38,40,41,45-50 and 52-74 is/are pending in the application.
- 4a) Of the above claim(s) 11,22,23,37,38,46-50,52-54 and 56-74 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,5,13,17,21,24,40,41 and 45 is/are rejected.
- 7) ☒ Claim(s) 12 and 55 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

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A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/20/05 has been entered.

Claims 2-4, 6-10, 14-16, 18-20, 25-36, 39, 42-44 and 51 have been canceled. Claims 1, 5, 11-13, 17, 21-24, 37, 38, 40, 41, 45-50, 52 and newly presented claims 53-74 are still at issue and are present for examination.

Applicants' arguments filed on 4/20/05, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Applicant's election with traverse of Group I, Claims 1, 5, 11-13, 17, 21, 24, 37, 38, 40, 41, 45, 52 and new claims 53-57 and of *glnAp2* as promoter species and isopentenyl diphosphate isomerase (*idi*) as heterologous polypeptide in the response filed 12/5/03 is acknowledged. Applicants request rejoinder of method claims 22, 23, 46-50, and 58-74 and claims to the non-

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elected species i.e., 11, 37, 38, 52-54, 56 and 57. However, The methods of Groups II (i.e., methods of producing an isoprenoid) and III (i.e., methods of producing lycopene) as defined in the lack of unity of 10/3/03 do not share any special technical feature with the products of Group I as many products within Group I cannot be used for the processes of Groups II and III. For example a *glnL*⁻ *E. coli* cell transformed with a polyketide synthase gene operably linked to the *glnAp2* promoter which is clearly a product within the scope of Group I cannot be used for the methods of either of groups II or III. Furthermore the claims to the non-elected species within group I remain withdrawn as the linking generic claims are not allowable over the art (see the rejections herein).

Claims 11, 22, 23, 37-38, 46-50, 52-54, 56 and 57-74 are withdrawn from further consideration pursuant to CFR 1.142(b) as being drawn to a nonelected invention (Claims 22, 23, 46-50, and 58-74) or species (Claims 11, 37, 38, 52-54, 56 and 57), there being no allowable generic or linking claim. Claims 1, 5, 12, 13, 17, 21, 24, 40, 41, 45 and 55 are examined herein.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see for example page 2 of the specification). Applicant is

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required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claims 13 and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 is confusing in the recitation of "the host cell of claim 17 wherein the enzyme is ... 1-deoxyxylulose 5-phosphate synthase" because claim 17 from which claim 13 depends limits the enzyme to an enzyme that catalyzes biosynthesis of an isoprenoid but the product of 1-deoxyxylulose 5-phosphate synthase (i.e., 1-deoxyxylulose 5-phosphate) is not an isoprenoid.

Claim 41 is confusing in the recitation of "the host cell of claim 40 wherein the biosynthetic enzyme is ... 1-deoxyxylulose 5-phosphate synthase or phosphoenolpyruvate synthase" because claim 40 from which claim 41 depends limits the biosynthetic enzyme to an enzyme that catalyzes biosynthesis of an isoprenoid, polyketide or polyhydroxyalkanoate but the products of 1-deoxyxylulose 5-phosphate synthase (i.e., 1-deoxyxylulose 5-phosphate) and phosphoenolpyruvate synthase (i.e., PEP) are not an isoprenoid, polyketide or polyhydroxyalkanoate.

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Claims 1, 5, 17, 21, 24, 40, and 45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *E. coli* having an inactivating *glnL* mutation which are transformed with a nucleic acid encoding one or more of the enzymes isopentenyl diphosphate isomerase, geranylgeranyl diphosphate synthase, 1-deoxyxylulose 5-phosphate synthase and phosphoenol pyruvate synthase operably linked to the *glnAp2* promoter, kits comprising an *E. coli* having a *glnL* mutation and a nucleic acid encoding the *glnAp2* promoter or nucleic acid constructs therefore, does not reasonably provide enablement for *E. coli* having an inactivating *glnL* mutation which are transformed with a nucleic acid encoding any biosynthetic enzyme for the production of any isoprenoid, any polyketide or any polyhydroxyalkanoate. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

These claims are so broad as to encompass any *E. coli* having an inactivating *glnL* mutation which are transformed with a nucleic acid encoding any biosynthetic enzyme for the production of any isoprenoid, any polyketide or any polyhydroxyalkanoate and the use of such cells for the production of any isoprenoid, any polyketide or any

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polyhydroxyalkanoate. The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of genes necessary for the construction of the host cells broadly encompassed by the claims nor for the use of all such cells for the production of any isoprenoid, any polyketide or any polyhydroxyalkanoate.

Isoprenoids, polyketides and polyhydroxyalkanoates each encompass an enormous family of highly complex compounds which are synthesized by highly complex biosynthetic pathways by an enormous number of different enzymes many of which are present in only a small number of microorganisms. Furthermore, wild type *E. coli* do not produce any polyketides or polyhydroxyalkanoates and produce only a very limited number of isoprenoids. Furthermore, while genes for the synthesis of some isoprenoids, polyketides and polyhydroxyalkanoates are provided by the specification and/or prior art, use of any combination thereof for the production of any isoprenoid, polyketide or polyhydroxyalkanoate is not a straightforward process involving only the transformation of a single gene into *E. coli* and expression of this gene therein. For many isoprenoids, polyketides and polyhydroxyalkanoates to be produced multiple genes are necessary only some of which may be available in the prior art, the biosynthetic pathways as well as competing

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metabolic processes are not well defined, and all necessary precursors may not be present or may not be present in sufficient amounts. See for example the teachings of Kholisa et al. regarding the difficulties of expressing polyketides in *E. coli*. Thus, the art provides little predictability of which isoprenoids, polyketides and polyhydroxyalkanoates can be produced using the teaching of the specification. Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any *E. coli* having an inactivating *glnL* mutation which are transformed with a nucleic acid encoding any biosynthetic enzyme for the production of any isoprenoid, any polyketide or any polyhydroxyalkanoate and the use of such cells for the production of any isoprenoid, any polyketide or any polyhydroxyalkanoate. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of bacterial cells having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 1, 5, 40, and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over either of Khosla et al. (US PG-PUBS 2002/0045220) or in view of Bock et al. (US Patent 5,830,692), McCleary et al. (Reference AL of applicant's PTO-1449), McCleary et al. (Reference AM of applicant's PTO-1449) and Haldiman et al. (Reference AK of applicant's PTO-1449) or Feng et al. (Reference AJ of applicant's PTO-1449).

Khosla et al. teach constructs for the recombinant expression of polyketide synthase modules in *E. coli* cells for the production of polyketides. The constructs of Khosla et al. comprise the polyketide synthase gene under the control of the inducible lac promoter. (see Fig 6). Khosla et al. further teach that the initial precursors of all polyketides include acetyl-CoA.

Bock teach that inducible promoters such as lac, tac, and trp promoters possess several disadvantages in relation to their use for industrial production. These are that the repressors and inducers necessary for use of these promoters are expensive and difficult to handle, particularly when they are metabolizable substances (such as lactose and tryptophan), and cannot be induced completely when the repressor is present in molar excess. (see columns 1-2).

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McCleary (AK) and McCleary (AP) teach that acetyl phosphate may act a global regulatory signal in *E. coli* responsible for the activation of a wide range or response regulators of two-component systems, including the *glnAp2* promoter, in the absence of their cognate histidine kinase (i.e., the *ntrB* gene product in the case of *glnAp2*). They further teach that acetyl-phosphate levels in bacteria correlate with the amount of acetyl-CoA produced and is present at high levels whenever glycolytic intermediates accumulate.

Haldiman et al. and Feng et al. each teach *E. coli* two-component system promoters (the *VanH* promoter in Haldiman et al. and the *glnAp2* promoter in Feng et al.) which are activated by a response regulator protein (*VanR* in Haldiman et al. and *NtrC* in Feng et al.) and acetyl phosphate in the absence of the corresponding histidine kinases (*VanS* in Haldiman et al. and *NtrB* in Feng et al.) and in the presence or absence of nitrogen.

As inducers (IPTG) for promoters such as *lac* used by Khosla et al. are expensive and have disadvantages as taught by Bock, it would have been obvious to one of ordinary skill in the art to link the production of the polyketide synthase to the presence of a metabolite in the cell which signals that significant amounts of the precursors for polyketide biosynthesis are present. McCleary et al. (1993) teach that

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acetyl phosphate accumulation occurs under these conditions. Therefore, it would have been obvious to one of ordinary skill in the art to replace the *lac* promoters in the constructs of Khosla et al. with a promoter which is induced by high acetyl phosphate levels. As McCleary et al. (AK and AP) teach that acetyl-phosphate levels correlate with the amount of acetyl-CoA produced, it would have been obvious to one of ordinary skill in the art to link the polyketide synthase genes of Khosla et al. to the acetyl-phosphate regulated promoters taught by Haldiman et al. or Feng et al. and express these constructs in *E. coli* cells which lack the cognate histidine kinases such that the response regulators which activate transcription from these promoters are activated by acetyl phosphate. Furthermore, it would have been obvious to one of ordinary skill in the art to put the cells and vectors necessary for production of high levels of polyketides together in a kit for easy handling.

Claims 12 and 55 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca E. Prouty whose telephone number is 571-272-0937. The examiner can normally be reached on Tuesday-Friday from 8 AM to 5 PM. The examiner can also be reached on alternate Mondays

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A handwritten signature in black ink, appearing to read 'Rebecca Prouty', with a stylized, flowing script.

Rebecca Prouty
Primary Examiner
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